Amendments to the Claims

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1(Currently amended). ~~An isolated DNA molecule according to claim 29~~, The method of claim 38 wherein said heterologous polypeptide contains a non-native apical surface membrane targeting sequence.

Claims 2-6 (Cancelled)

7(Currently amended). ~~An isolated DNA molecule according to~~ The method of claim 1, wherein said non-native apical surface membrane targeting sequence is a C-terminal glycosyl phosphatidylinositol (GPI) signal sequence.

8(Currently amended). ~~An isolated DNA molecule according to~~ The method of claim 1, wherein said apical surface membrane targeting sequence is one or more non-native sites for glycosylation at predicted β-turns of said heterologous polypeptide.

9(Currently amended). ~~An isolated DNA molecule according to~~ The method of claim 8, wherein said one or more non-native sites for glycosylation are sites for Asn-linked glycosylation.

10(Currently amended). ~~An isolated DNA molecule according to~~ The method of claim 8, wherein said one or more non-native sites for glycosylation are sites for O-glycosylation.

Claim 11 (Cancelled)

12(Currently amended). ~~An isolated DNA molecule according to~~ The method of claim 1, wherein said heterologous polypeptide is a fusion polypeptide.

13(Currently amended). ~~An isolated DNA molecule according to~~ The method of claim 12, wherein said fusion polypeptide is a fusion between a heterologous polypeptide of interest and uromodulin via a chemically or enzymatically cleavable linker, said uromodulin having a GPI signal sequence at its C-terminus.

14(Currently amended). ~~An isolated DNA molecule according to~~ The method of claim 13, wherein said linker is a protease-sensitive linker.

15(Currently amended). ~~An isolated DNA molecule according to~~ The method of claim 1, further comprising a DNA sequence encoding phosphatidylinositol-specific phospholipase C (PIPLC), wherein said DNA sequence is disposed downstream of said heterologous DNA sequence and is operably linked to said mammalian uromodulin promoter, whereby said mammalian uromodulin promoter is capable of driving the expression of said DNA sequence encoding PIPLC.

16(Currently amended). ~~An isolated DNA molecule according to~~ The method of claim 1, wherein any basolateral surface membrane targeting signals native to said heterologous polypeptide is inactivated or deleted.

Claims 17-24 (Cancelled)

25(Currently amended). A transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant construct

corresponding to [[the]] a DNA molecule ~~of claim 1~~ comprising a mammalian uromodulin promoter operably linked to a heterologous DNA sequence encoding a heterologous polypeptide, wherein:

said mammalian uromodulin promoter directs expression of said heterologous polypeptide *in vivo* to the ascending limb of Henle's loop and the early distal tubules of the kidneys to produce a recombinant biologically active polypeptide in the urine[[,]];

said DNA molecule ~~having~~ has been introduced into said mammal [[is]] selected from the group consisting of goat, sheep, [[cow]] cattle, pig and mouse ~~and, or an ancestor of said mammal~~, at an embryonic stage[[,]]; and ~~wherein~~

said mammal produces recoverable amounts of a recombinant biologically active polypeptide in its urine.

Claims 26 and 27 (Cancelled)

28(Currently amended). A transgenic non-human mammal according to claim 25, in which all germ cells and somatic cells further contains a recombinant construct comprising a mammalian uromodulin promoter operably linked to a DNA sequence encoding PIPLC, wherein said mammalian uromodulin promoter expresses PIPLC in the kidneys of said transgenic mammal.

Claims 29-37 (Cancelled)

38(Currently amended). A method for producing a recombinant biologically active polypeptide, comprising:

introducing [[the]] an isolated DNA molecule ~~of claim 29,~~ comprising a mammalian uromodulin promoter operably linked to a heterologous DNA sequence encoding a heterologous polypeptide, wherein said mammalian uromodulin promoter directs expression of said heterologous polypeptide *in vivo* to the ascending limb of Henle's loop and the early distal tubules of the kidneys to produce a recombinant biologically active polypeptide in the urine, into a fertilized embryo of a non-human mammal selected from the group consisting of goat, [[cow]] cattle, sheep, pig, and mouse to generate a transgenic non-human mammal which expresses and secretes the heterologous polypeptide into the urine of the transgenic non-human mammal as a recombinant biologically active polypeptide;

collecting urine from the transgenic non-human mammal; and

recovering the secreted polypeptide to produce a recombinant biologically active polypeptide.

39(Original). A method according to claim 38, wherein said introducing step comprises injecting the isolated DNA molecule into a pronucleus of a fertilized embryo.

Claim 40(Cancelled).

41(Currently amended). A method according to claim [[40]] 38, wherein the mammalian uromodulin promoter is a mouse, goat, bovine, [[pig]] human or rat uromodulin promoter.

42(Currently amended). A method according to claim [[40]] 38, wherein the mammalian uromodulin promoter is a goat uromodulin promoter.

Claims 43-45 (Cancelled)

46(Currently amended). A transgenic non-human mammal according to claim [[44]] 25, which is a transgenic goat.

Claim 47(Cancelled).

48(Currently amended). A method according to claim [[40]] 38, wherein the mammalian uromodulin promoter is a mouse uromodulin promoter.

49(Previously presented). A method according to claim 38, wherein said non-human mammal is a goat.

50(Currently amended). A method according to claim 38, wherein said non-human mammal is [[a cow]] cattle.

Claim 51(Cancelled).

52(Currently amended). A ~~method~~ transgenic non-human mammal according to claim 25, wherein said non-human mammal is [[a cow]] cattle.

Claims 53-55(cancelled).

56(New). The transgenic non-human mammal of claim 25, wherein sad heterologous polypeptide contains a non-native apical surface membrane targeting sequence.

57(New). A method for producing a recombinant biologically active polypeptide, comprising:

introducing an isolated DNA molecule comprising a mammalian uromodulin promoter, selected from the group consisting of mouse, goat, human, rat, and bovine uromodulin promoters and operably linked to a heterologous DNA sequence encoding a heterologous polypeptide, into a fertilized embryo of a non-human mammal selected from the group consisting of goat, cattle, sheep, pig and mouse to generate a transgenic non-human mammal which expresses said heterologous polypeptide *in vivo* to the ascending limb of Henle's loop and the early distal tubules of the kidneys to produce and secrete the heterologous polypeptide into the urine of the transgenic non-human mammal as a recombinant biologically active polypeptide;

collecting urine from the transgenic non-human mammal; and

recovering the secreted polypeptide as a recombinant biologically active polypeptide.

58(New). A method according to claim 57, wherein said heterologous polypeptide contains a non-native apical surface membrane targeting sequence.

59(New). A transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant construct corresponding to a DNA molecule comprising a mammalian uromodulin, selected from the

group consisting of mouse, goat, human, rat and bovine uromodulin promoters and operably linked to a heterologous DNA sequence encoding a heterologous polypeptide, said DNA molecule having been introduced into said mammal selected from the group consisting of goat, sheep, cattle, pig and mouse at an embryonic stage, wherein said mammalian uromodulin promoter directs expression of said heterologous polypeptide *in vivo* to the ascending limb of Henle's loop and the early distal tubules of the kidneys to produce recoverable amounts of a recombinant biologically active polypeptide in its urine.

60(New). A transgenic non-human mammal according to claim 59, wherein said heterologous polypeptide contains a non-native apical surface membrane targeting sequence.